REVIEW DRAFT: CIRM Guidelines for Oocyte Donation for Stem Cell Research

Introduction

Stem cell research has the potential to discover and advance treatments for chronic disease and injury.[1] To realize this potential, researchers are working to improve the diversity and quality of human embryonic stem cells (hESCs) lines. hESCs lines are derived from human blastocysts created from oocytes. To date, hESCs have typically been derived from human blastocysts originally created for reproductive purposes by in-vitro fertilization (IVF).

Scientific Background

IVF procedures may also be used to create blastocysts for non-reproductive purposes. Blastocysts may be created for fundamental research to study basic biological mechanisms of early embryo development. Research aimed at developing cell therapies may utilize oocytes for nuclear transfer experiments. Nuclear transfer involves inserting the nucleus from a somatic cell (for example, a skin cell) into an oocyte from which the nucleus has been removed. To date, nuclear transfer experiments have been performed successfully in non-human animals and primates.[2] Stem cells derived from the resulting blastocysts are copies or "clones" of the original somatic cell because their nuclear DNA matches that of the donor cell. Therapeutic cloning through nuclear transfer has been proposed as a means of developing human cellular therapies immunologically-matched for the recipient. Alternatively, cloning cells from diseased individuals can be used to establish models to study the etiology of those diseases.[3]

Ethical Consideration

Demonstrating the feasibility of nuclear transfer in humans and making operational such methodologies will require the donation of human oocytes. For CIRM funded research, investigators will need to secure oocytes from women consenting to donation exclusively for research use. Such donation has raised ethical concerns since oocyte retrieval involves potential acute and long-term risk to the donor.[4] While oocyte donation has been performed for decades in the context of fertility treatments, donation for research will neither achieve pregnancy nor otherwise create direct therapeutic benefits to the donor or potential patients at this time. [5]

To address ethical concerns related to the use of human oocytes, CIRM has sponsored a number of initiatives designed to advance the safe conduct of CIRM-sponsored research. Efforts to date include:

- The development of comprehensive Medical and Ethical Standards regulations governing all CIRM-funded research. These regulations include a series of special requirements to protect oocyte donors.

- The sponsorship of scientific forums to support evidence-based policy. In 2006, CIRM commissioned the Institute of Medicine to convene a workshop titled *Assessing Risks of Oocyte Donation for Stem Cell Research.*[6] The workshop report suggested there are opportunities for minimizing medical risks in donors who provide oocytes exclusively for research.

Committee Charge

Building upon the IOM workshop and report, CIRM convened an advisory committee comprised of experts with clinical experience in reproductive medicine. The committee was charged with developing specific recommendations for reducing the risk of ovarian hyperstimulation syndrome (OHSS) and other acute complications that may occur

following oocyte donation. The recommendations are based upon published evidence in peer-reviewed literature, best practices, and best clinical judgment. The guidelines are intended to assist researchers in the design and IRB's in the evaluation of research protocols involving the donation of oocytes exclusively for research.

Statement of Principle

The IOM workshop and report discussed the unique ethical context in which research donation exists – women incur some medical risk without direct benefit to themselves or others. Because of this risk-benefit ratio the IOM committee advocated a "conservative" or cautious approach to research donation when otherwise healthy donors are involved. This committee concurs with the IOM that potential research donors should be evaluated in a conservative manner. Central to this approach is the identification of risk factors associated with a greater likelihood that a donor will develop OHSS or other complication. In practice, the identification of any clinically evidenced risk factor should be considered grounds for exclusion. This approach is more stringent than published guidelines for assisted reproduction where specific risk factors may be deemed acceptable in a woman undergoing IVF for her own reproductive benefit or that of another woman or couple.

These guidelines draw on peer-reviewed literature, best practices and the clinical judgment of the authors to identify individual characteristics that would result simultaneously in a high chance of successful donation and a low probability of adverse health events. The committee recognizes that it may be appropriate to reevaluate specific recommendations in light of new evidence.

Further, the committee also recognizes that developments in stem cell science may shift the risk-benefit ratio thus altering the ethical context of research donation. For example, if the clinical utility of nuclear transfer is demonstrated in humans, there may be circumstances where donors incur more direct benefit, such as access to potent new therapies for themselves, their family members or others. Similar consideration should

be given to potential donors with diseases that may be the subject of study as a result oocyte donation. Under such circumstances, ethically appropriate proposals may deviate from these current recommendations. The IRB should evaluate the rationale for such deviation and judge accordingly consistent with their duty to determine whether risks are reasonable and consistent in relation to anticipated benefits.[7]

Framework for OHSS and Acute Outcome Risk Reduction

The goal of these guidelines is to identify donor characteristics which, in the committee's judgment, would result in a high chance of successful donation and a low probability of adverse health events. Towards these ends, the committee recommends the application of a four-point framework designed to coincide with clinical opportunities for donor screening and evaluation. Specific guidelines for exclusion are contained in the corresponding tables.

1. Pre-induction screening exclusion criteria (Table 1)
    - Medical history
    - Targeted diagnostics to identify potential risk factors
2. Early ovulation induction monitoring (days 1-7 [Table 2])
    - Dosing recommendations
    - Day 2-3 indicators
    - Indicators of hyper-response
    - Indicators of hypo-response
3. Oocyte Aspiration (Table 3)
    - Method and certification
    - Recommended protocols
4. Post-aspiration surveillance (Table 4)
    - Short term
    - Menses check

1. Pre-induction screening exclusion criteria [8, 9, 10, 11]	
(1a.) Medical history	1. Single ovary 2. Previous history of OHSS 3. History of thrombosis / bleeding diathesis / familial thrombophilia 4. Uncontrolled hypertension / diabetes 5. ASA III anesthetic risk 6. History of estrogen sensitive cancers 7. History of ovarian tumors of low malignant potential (LMP or borderline) or malignancies 8. History of PID requiring hospitalization
(1b.) Exclusionary Diagnostics	9. BMI > 30 [12] 10. Advanced maternal age 11. Elevated or diminished AMH; elevated day 2 or 3 FSH and/or estradiol 12. Antral follicle count greater than 12 13. Endometrioma or stage III-IV endometriosis 14. Any abnormal tubo-ovarian morphology (hydrosalpinx) or uterine morphology (fibroids) that impacts access on ultrasound for retrieval 15. Inability to tolerate ultrasound or pelvic examination 16. High vaginal pH (greater than 4.5)

2. Early ovulation induction monitoring [9, 13]	
(2a) Dosing recommendations (days 1-7)	1. General recommendations: • Starting dose 150 IU if age less than 30 • 225 IU amps if age 30-40 2. Maintain starting dose for first at least first five days of stimulation
(2b) Day 2-3 indicators	3. Elevated FSH and E2 levels may predict poor response
(2c) Indicators for stopping (hyper-response [after day 7])	4. Greater than 1,000 pg/mL estradiol and/or more than twenty 12mm follicles count on day 6 of stimulation
	5. E2 greater than 3,000 pg/mL on day of hCG administration
(2d) Indicators for stopping (hypo-response [on day 7])	6. Consider cancel if less than 3 active growing follicles

3. Oocyte Aspiration	
(3a) Method & Certification	1. Retrieval by experienced IVF physician; Conscious sedation recommended under the care of a board certified anesthesiologist.
(3b) Recommended protocols	2. Consider avoiding aspirin-containing medications two weeks prior to retrieval.
	3. NSAIDs should be used for post procedure pain

4. Post-Aspiration Surveillance	
(4a) Short term	1. If patient calls because of symptoms, she must be seen within 24 hours.
(4b) Menses check	2. Call with menses, if no menses two weeks post-retrieval then pregnancy test

The tables identify exclusionary criteria to be considered in donor screening and monitoring protocols. For certain indicators, where there is sufficient support in the literature, quantitative criteria are recommended. For some criteria it is not possible to recommend quantitative criteria at this time. For such criteria, it is incumbent on the practitioners to take develop procedures and policies based on their own clinical experience. These guidelines attempt to provide sufficient specificity to assist researchers in the design and IRBs in the evaluation of research protocols.

Specifically normal range values for AMH (change this globally, now the preferred term for MIS), FSH, estradiol and antral follicle count may vary between programs and therefore it is difficult to provide value guidelines recognizing that assay performance can vary and absolute risk is dependent on factors specific to the hormone therapy. The committee also refrained from providing a recommendation regarding polycystic ovary syndrome. Some reports have suggested that OHSS risk is highest in women with PCOS-like characteristics.[14] The committee feels the strength and consistency of a possible association is insufficient to warrant a specific recommendation. As with all women undergoing an IVF cycle, the baseline ultrasound scan and antral follicle count should be combined with an appropriately dosed stimulation protocol to ensure safety.

Comment on Infectious Disease Screening

There is uncertainty regarding the relationship between specific infectious diseases and adverse medical outcomes from retrieval. Rarely Chlamydia, gonococcus or bacterial vaginosis affect risk for upper tract infection in donors. High vaginal pH (greater than 4.5) is an indicator of bacterial vaginosis. Bacterial vaginosis can be transmitted to the upper tract and may confer an increased risk of pelvic infection during ovary puncture.[10, 15] All the infectious diseases identified previously should be treated before a potential donor is considered.

FDA requires also donor screening and specimen testing for infectious disease. Infectious disease screening is important for the protection of laboratory personnel who handle biological samples. Screening requires a review of relevant medical records, including a donor medical history interview and physical exam. The screening for donors of reproductive cells or tissues must specifically address risk factors for, and evidence of:

- HIV
- Hepatitis B
- Hepatitis C
- Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob
- Treponema pallidum;
- Communicable disease risks associated with xenotransplantation
- Chlamydia trachomatis; and Neisseria gonorrhea

While none of the outcomes identified in the above screening tests are identified risk factors for acute outcomes in oocyte donation, these guidelines seem prudent. Another consideration discussed by the panel was the relative contraindication of donors with a history of chronic pelvic pain. In some circumstances women with such a history should be allowed to participate in oocyte donation, but clinical judgment should be cautious as

exacerbation of chronic pelvic pain could be misconstrued as an acute procedure related complication.

Comment on Registries and Long-Term Donor Tracking

The committee concurs with the observation in the IOM report that the absence of registries to track the health of oocyte donors represents a limitation for evaluating any long-term effects. There is a need for additional data that would be applicable to the population in question – ostensibly healthy donors who are not intending to undergo IVF at time of donation. Evidence suggests that oocyte donation that is performed exclusively for research is rare presently, thus raising questions about our ability to compile data with sufficient statistical power to draw valid inference. As stem cell research advances there may be opportunities to compile additional data; however, in all likelihood such a registry system would require coordination of a multiple centers.

Need for Ongoing Evaluation

These guidelines support a precautionary approach to oocyte donation exclusively for research. Specific recommendations are based on published evidence, best practices and the committee's best judgment at the time of publication. The committee recognizes that ongoing developments in the field of reproductive medicine may produce evidence that warrants a reevaluation of specific recommendations.

Committee Members:

Valerie Montgomery Rice, MD	vmontgomery-rice@mmc.edu
Robert N. Taylor, MD, PhD,	robert.n.taylor@emory.edu
Mark V. Sauer, M.D. (we're all FACOGs)	mvs9@columbia.edu
David A. Eschenbach, MD	eschen@u.washington.edu
Sandra A. Carson, MD	SCarson@WIHRI.org
Committee Staff:	
Dr. Geoffrey Lomax	glomax@cirm.ca.gov

1. CIRM. CIRM scientific strategic plan San Francisco: CIRM; 2006.
2. Byrne J, Pedersen D, Clepper L, et al. Producing primate embryonic stem cells by somatic cell nuclear transfer. Nature 2007.
3. Gruen L, Grabel L. Concise review: scientific and ethical roadblocks to human embryonic stem cell therapy. Stem Cells 2006;24(10):2162-9.
4. Pennings G, de Wert G, Shenfield F, Cohen J, Tarlatzis B, Devroey P. ESHRE Task Force on Ethics and Law 12: oocyte donation for non-reproductive purposes. Hum Reprod 2007;22(5):1210-3.
5. IOM. Assessing the medical risk of human oocyte donation for stem cell research: workshop report. Washington, D.C.: The National Academies Press; 2007.
6. IOM. Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research. In: Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research. San Francisco; 2006.
7. DHHS. Federal policy for the protection of human subjects. In; 1991.
8. Ovarian hyperstimulation syndrome. Fertil Steril 2006;86(5 Suppl):S178-83.
9. Mathur R, Kailasam C, Jenkins J. Review of the evidence base of strategies to prevent ovarian hyperstimulation syndrome. Hum Fertil (Camb) 2007;10(2):75-85.
10. Kavoussi SK, Pearlman MD, Burke WM, Lebovic DI. Endometrioma complicated by tubo-ovarian abscess in a woman with bacterial vaginosis. Infect Dis Obstet Gynecol 2006;2006:84140.
11. Rizk B. Ovarian hyperstimulation syndrome : epidemiology, pathophysiology, prevention and management. Cambridge ; New York: Cambridge University Press; 2006.
12. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology a systematic review. Hum Reprod Update 2007;13(5):433-44.
13. Jayaprakasan K, Herbert M, Moody E, Stewart JA, Murdoch AP. Estimating the risks of ovarian hyperstimulation syndrome (OHSS): implications for egg donation for research. Hum Fertil (Camb) 2007;10(3):183-7.
14. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update 2002;8(6):559-77.
15. Ness RB, Kip KE, Hillier SL, et al. A cluster analysis of bacterial vaginosis-associated microflora and pelvic inflammatory disease. Am J Epidemiol 2005;162(6):585-90.

Exclusion for Medical History

- ☐ Single ovary
- ☐ Previous history OHSS
- ☐ History of thrombosis / bleeding diathesis / familial thrombophilia
- ☐ Uncontrolled hypertension / diabetes
- ☐ ASA III anesthetic risk
- ☐ Estrogen-sensitive cancers or borderline ovarian tumors

Exclusion Diagnostics

- ☐ Advanced age
- ☐ BMI > 30
- ☐ Elevated or diminished AMH
- ☐ Advanced endometriosis
- ☐ Abnormal tubo-ovarian morphology (hydrosalpinx) or uterine morphology (fibroids) on ultrasound that impact retrieval access
- ☐ High vaginal pH (greater than 4.5)
- ☐ Virginal introitus

Dosing

- ☐ General recommendations (starting dose 2 amps if age less than 30, 3 if age 30-40)
- ☐ Maintain starting dose for at least first five days of stimulation

Stopping Hyper-response

- ☐ Greater than 1000 pg estradiol and/or more than 20 x 12mm follicle count on day 6 of stimulation
- ☐ E2 greater than 3,000 pg/ml on day of hCG

Stopping Hypo-response

- ☐ Elevated FSH & E2 may predict poor response
- ☐ Consider cancel if less than 3 active growing follicle

Aspiration

- ☐ Conscious sedation recommended under the care of a board-certified anesthesiologist
- ☐ Aspirin containing medications and other anti-platelet drugs should be avoided for up to two weeks prior to retrieval
- ☐ NSAIDs should be used for pain

Short term Surveillance

- ☐ If donor calls with symptoms, she must be seen
- ☐ Call with menses, if no menses two weeks post-retrieval then pregnancy test